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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,266	05/23/2000	William G. Johnson	601-1-057N	4282

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EXAMINER
MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
1631	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/577,266	Applicant(s) JOHNSON ET AL.	
	Examiner Marjorie A. Moran	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,24-27 and 29-47* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 30-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21,24-27 and 29-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Election/Restrictions

This application contains claims 1-18 and 30-47, drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-18 and 30-47 are again withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claims 1-21, 24-27, and 29-47 are pending. An action on the merits of elected claims 19-21, 24-27, and 29 follows. All rejections and objections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 recites a method of treating an individual determined by the method of claim 21 "to be susceptible for developing a developmental disorder". However, parent claim 19 is directed to a method for determining the susceptibility of an individual to

have offspring that develop a developmental disorder, not for a method of determining the susceptibility of the individual herself to develop a developmental disorder. As it is unclear which "individual" is intended to be "susceptible" to develop a disorder and/or be the recipient of treatment; i.e. the pregnant woman or her offspring, claim 29 is indefinite.

Claim 29 recites treatment of an "asymptomatic" individual. As the developmental disorder of parent claim 21 is one which may be developed by an offspring of the individual being assessed, and the parent presumably does not have the disorder, it is unclear what "symptoms" an individual is intended to be "asymptomatic" for in order for treatment to occur in the method of claim 29. For this reason, claim 29 is further indefinite.

For purposes of applying the prior art, claim 29 will be treated as if it recites a method of administering methylfolate, cobalamin, or pyridoxine to an individual identified in the method of claim 21 to be susceptible to having offspring that develop a developmental disorder.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 19 is rejected under 35 U.S.C. 102(a) as being anticipated by CHRISTENSON et al. (Am. J. Med. Genetics (5/21/1999) vol. 84 (2), pp. 151-157).

CHRISTENSEN teaches a method of estimating the susceptibility of pregnant woman to have children with a neural tube defect (NTD) by analyzing nucleic acids and determining the presence of polymorphic alleles of MTHFR and MTR in both mothers and offspring (pp. 152-154), adding this dataset to a reference (control) dataset (p. 153-154, Tables I and III), formulates a model based on his combined datasets (p. 156), and predicts the probability (odds ratio) for any woman to have children with NTD's based on the genetic data (p. 154, Table II). CHRISTENSEN specifically teaches analysis of his data by logistic regression (p. 154). CHRISTENSEN also predicts the risk for woman having a child with an NTD based on environmental factors (p. 155, Fig. 1), and teaches that a combination of genetic and environmental variables increases the risk of mothers having a child with an NTD (p. 156), therefore the total teaching of CHRISTENSEN anticipates claim 19.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157).

Applicant's arguments with respect to claims 19-21 have been considered but are moot in view of the new ground(s) of rejection.

Claim 19 recites a method of estimating the probability of a pregnant woman to have offspring which develop a developmental disorder comprising collecting a biological sample containing nucleic acids or protein from one or more subjects, analyzing the nucleic acids or proteins to generate a genotype of alleles associated with folate, pyridoxine and/or cobalamin metabolism, adding the resultant dataset(s) from each subject to a reference dataset, formulating a model based on the subject dataset(s), then analyzing the combined dataset by binary logistic regression to determine a predicted probability for the woman to have offspring which develop a developmental disorder and to estimate a genetic and environmental susceptibility of the individual toward having offspring which develop a developmental disorder. Claim

20 limits the model to an added step of adding or subtracting a genetic variable, re-analyzing data, and choosing a model which best fits the data. Claim 21 recites testing the model for goodness of fit.

CHRISTENSEN teaches a method of estimating the probability of a pregnant woman to have a child with an NTD, as set forth above. CHRISTENSEN teaches measurement of two genetic variables, MTHFR and MTR (Tables I and III), and thus suggests adding the MTR genetic variable to his MTHFR data. AS CHRISTENSEN determines that MTR has little or negative affect on the probability of a woman having a child with an NTD (pp. 154-155), and his subsequent model does not include MTR data (Tables IV and V), CHRISTENSEN suggests "choice" of a model which best fits his data; i.e. one which does not include MTR data. CHRISTENSEN's teaching for confidence intervals and calculation of statistical significance suggest teaching of "testing" his model for goodness of fit. CHRISTENSEN does not specifically teach choosing a model which best fits his data nor testing his model for goodness of fit.

It would have been obvious to one of ordinary skill in the art at the time of invention to have chosen a model in the method of CHRISTENSEN which best fits his data for estimating the odds of a woman having a child with an NTD, as suggested by the teachings of CHRISTENSEN that an MTR polymorphism probably is NOT a marker for the probability of a child having and NTD, where the motivation would have been to most accurately predict the probability thereof, as suggested by the totality of CHRISTENSEN's teachings. In addition, it would have been obvious to have tested the model in the method of CHRISTENSEN for goodness of fit to his data, as suggested by

CHRISTENSEN's statistical analysis, where the motivation would have been to give the best prediction of risk based on known genetic and environmental variables, as taught by CHRISTENSEN (p. 156).

Claims 24-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) as applied to claims 19-21 above, and further in view of ROZEN et al. (IDS ref: US 6,218, 120, filed 3/1/1999).

Claims 24 and 29 (see above) recite a method of lowering the risk of a woman to have offspring with a developmental disorder, as predicted in the method of claim 21, by administering methylfolate, cobalamin, or pyridoxine to the woman.

CHRISTENSEN teaches and makes obvious a method of estimating the probability of a pregnant woman to have a child with an NTD, wherein a best fit to data is determined, as set forth above. CHRISTENSEN specifically teaches monitoring folate, cobalamin and homocysteine concentrations in his method (pp. 154-156), and teaches administration of folic acid to women (p. 151, abstract). CHRISTENSEN does not specifically teach administering methylfolate, cobalamin or pyridoxine.

ROZEN teaches that deficiency in methyltetrahydrofolate (MTHFR) can lead to various disorders wherein folate administration to women is known to reduce NTD's in offspring (col. 2, lines 32-45), thus suggesting administration of MTHFR to pregnant woman at risk of having children with NTD's.

It would have been obvious to one of ordinary skill in the art at the time of invention to have administered the MTHFR of ROZEN to women determined to be at risk for having children with NTD's in the method of CHRISTENSEN where the motivation would have been to administer a type of folic acid known to reduce the incidence of NTD's, as suggested by ROZEN.

Claims 24-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) as applied to claims 19-21 above, and further in view of SARILL et al. (US 6,274,564, filed 9/17/1997).

Claims 24 and 29 (see above) recite a method of lowering the risk of a woman to have offspring with a developmental disorder, as predicted in the method of claim 21, by administering methylfolate, cobalamin, or pyridoxine to the woman.

CHRISTENSEN teaches and makes obvious a method of estimating the probability of a pregnant woman to have a child with an NTD, wherein a best fit to data is determined, as set forth above. CHRISTENSEN specifically teaches monitoring folate, cobalamin and homocysteine concentrations in his method (pp. 154-156), and teaches administration of folic acid to women (p. 151, abstract). CHRISTENSEN does not specifically teach administering methylfolate, cobalamin or pyridoxine.

SARILL teaches periconceptual supplementation with vitamin B12 (cyanocobalamin) or cobalamin to prevent or decrease the incidence of neural tube defects (col. 7, lines 23-43).

It would have been obvious to one of ordinary skill in the art at the time of invention to have administered the vitamin B12 or cobalamin of SARILL to women determined to be at risk for having children with NTD's in the method of CHRISTENSEN where the motivation would have been to administer a compound known to reduce the incidence of NTD's, as taught by SARILL.

Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHRISTENSON et al. (Am. J. Med. Genetics (5/1/19990 vol. 84 (2), pp. 151-157) as applied to claims 19-21 above, and further in view of SCHOLL (IDS ref: Am. J. Clin. Nutrition (1996) vol. 63, pp. 520-525).

Claim 25 recites a method of determining of a treatment is advisable for a woman at risk for having offspring with a developmental disorder, as predicted in the method of claim 21, by measuring the concentration of a risk factor from a tissue sample or body fluid of the pregnant woman and determining that treatment is advisable when the concentration of risk factor is above or below an accepted range. Claim 26 recites a method of monitoring the effect of administering methylfolate, cobalamin or pyridoxine to the woman of claim 25. Claim 27 limits the risk factor of claims 25 and 26 to be homocysteine, folate, or cobalamin.

CHRISTENSEN teaches and makes obvious a method of estimating the probability of a pregnant woman to have a child with an NTD, wherein a best fit to data is determined, as set forth above. CHRISTENSEN specifically teaches measurement of folate, cobalamin and homocysteine concentrations in his method (pp. 154-156), and

teaches administration of folic acid to women (p. 151, abstract). CHRISTENSEN further teaches that mothers with low RBC folate (in the lowest quartile) are at risk for having children with NTD's (Fig. 1), thus suggesting that those with folate concentrations below an accepted range be treated. CHRISTENSEN does not teach monitoring the effect of treatment with folate, cobalamin or pyridoxine..

SCHOLL teaches monitoring the effect of administering folate to pregnant women (abstract), teaches that periconceptual use of folate is known to reduce incidence of NTD's (p. 520), and teaches that low folate levels are associated with low birth weight and preterm delivery (Tables 2, 3, 4).

It would have been obvious to one of ordinary skill in the art at the time of invention to have monitored the folate levels of pregnant women, as taught by SCHOLL, in the method of CHRISTENSEN, where the motivation would have been to ensure adequate levels of folate to reduce/prevent a host of teratogenic/prenatal complications, including development of NTD's, low birth weight and preterm delivery.

Conclusion

Claims 19-21, 24-27 and 29 are rejected, claims 1-18 and 30-47 are withdrawn.

The art made of record and not relied upon which is considered pertinent to applicant's disclosure is WILSON et al. (Molecular Genetics and Metabolism (Aug. 1999), vol. 67 (4), pp. 317-323.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703)

305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3524.

MARJORIE MORAN
PATENT EXAMINER

February 24, 2003